PATENT
Attorney Docket No. EURA-004/00US
(Formerly 451194-101)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Gopi M. Venkatesh et al.

Application No.: 10/713,929 Confirmation No.: 4820

Filed: November 14, 2003 Group Art Unit: 1615

For: MODIFIED RELEASE DOSAGE FORMS OF SKELETAL MUSCLE RELAXANTS Examiner: BARHAM, Bethany P.

DECLARATION UNDER 37 C.F.R. § 1.131

We, Dr. Gopi Venkatesh and James M. Clevenger declare as follows:

1. We are the named inventors of the above-noted application (Ser. No. 10/713,929)

2. We have read and understood the Official Action of January 11, 2008, and in particular the rejection of the pending claims under 35 U.S.C. §103 over the combination of U.S. Publ. No. 2004/0197407 (the '407 application) and U.S. Publ. Nos. 2003/0215496 or 2003/0099711.

3. We understand that the earliest asserted priority date of the '407 application is February 11, 2003, through the priority claim to U.S. Provisional Application Ser. No. 60/446,425.

4. The subject matter of the pending claims of the present application was invented by Gopi Venkatesh and James M. Clevenger (the named inventors) prior to February 11, 2003.

5. Example 3 of the instant application describes the formulation and production of a multiparticulate dosage form of cyclobenzaprine, wherein the cyclobenzaprine is coated on sugar spheres and covered with a water insoluble polymer to produced extended release beads (see paragraph 0045). Figure 4 of the instant application shows the release rate of the finished beads of Example 3 (e.g., **Batch 805-AAA-105).**

6. Exhibit A, dated before February 11, 2003, shows a "Master Formula" sheet documenting the production of the intermediate cyclobenzaprine coated beads used to make **Batch 805-AAA-105**. This intermediate batch (designated **Lot No. 837-AG-034**) comprises:

- "Sugar Spheres" (5475 g) coated with "cyclobenzaprine HCl" (1875 g) from "Acetone, NF 50/50% Ratio" and "USP Purified Water, 50/50% Ratio";
- seal coated with "2.00"% of "Opadry Clear YS-1-7006".

Exhibit B, dated before February 11, 2003, shows a "Master Formula" sheet documenting the actual production of **Batch 805-AAA-105** by coating the intermediate cyclobenzaprine beads of **Lot No. 837-AG-034** with an extended release water insoluble polymer:

- ER coating of **Lot No. 837-AG-034** with "Ethylcellulose 10P Premium (10 cps)" (363.6 g) and "Diethyl Phthalate" (36.4 g) dissolved in "Acetone, NF (98 parts) " and "USP Purified Water (2 parts)". Samples were collected with a coating weight of "10%" (designated **Batch or Lot No. 805-AAA-105**).

Exhibit C, dated before February 11, 2003, shows data for the mean cumulative release rate of cyclobenzaprine over time for "Lot # 805-AAA-105-10" (i.e., 10 wt.% ER coating, Batch 805-AAA-105). The data are identical to that presented in graphical form for the sample designated "10% ER Coating Wt., Batch 805AAA105" in Figure 4 of the instant application and shows that the 10% ER coated beads exhibit a release profile that after 2 hours, no more than about 40% of the total active is released; after 4 hours, from about 40-65% of the total active is released; after 8 hours, from about 60-85% of the total active is released; and after 12 hours, from about 75- 85% of the total active is released, wherein said dosage form is dissolution tested using United States Pharmacopoeia Apparatus 2 (paddles @ 50 rpm) in 900 mL of 0.1N HCl at 37°C. This is the same dissolution profile required by the pending claims.

7. Exhibit D, dated before February 11, 2003, is a batch record showing the ingredients of "Cyclobenzaprine HCl ER Beads", **Lot No. PE271EA001**:

- "Cyclobenzaprine HCl Intermediate Beads", Item code **PE249**; coated with "Ethylcellulose" and "Diethyl Phthalate".

Exhibit E, dated before February 11, 2003, documents the manufacture of "Cyclobenzaprine HCl MR Capsules, 30 mg", **Lot No. PF306EA001**:

- "White, Opaque Hard Gelatin Capsules, Size 4", filled with "Cyclobenzaprine HCl Extended Release Beads", Item code **PE271**.

Exhibit F, dated before February 11, 2003, shows data for the mean cumulative release rate of cyclobenzaprine over time for clinical batch "Lot # PF306EA001". The data are identical to that presented in graphical form for the clinical sample designated "PF306EA001" in Figure 6, Examples 4 and 5 of the instant application. Formulation PF306EA001 shows a release profile that after 2 hours, no more than about 40% of the total active is released; after 4 hours, from about 40-65% of the total active is released; after 8 hours, from about 60-85% of the total active is released; and after 12 hours, from about 75- 85% of the total active is released, wherein said dosage form is dissolution tested using United States Pharmacopoeia Apparatus 2 (paddles @ 50 rpm) in 900 mL of 0.1N HCl at 37°C. This is the same dissolution profile required by the pending claims.

8. Thus, Exhibits A and B document the production of the identical multi-particulate cyclobenzaprine dosage forms described in Example 3 of the present application, and as set forth in the instant claims, before February 11, 2003.

9. Thus, Exhibits D and E document the production of the identical clinical batch described in Examples 4 and 5 of the present application, and as set forth in the instant claims, before February 11, 2003.

10. We further declare that all statements made herein on our own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code, and that

such willful false statements may jeopardize the validity of the above-referenced application or any patent issuing thereon.

Respectfully submitted,

G.m Venkatesh
Gopi Venkatesh

2/13/2008
Date

James M. Clevenger
James M. Clevenger

2/13/2008
Date

Master Formula

Page ——— of ———

Product Name: Cyclobenzaprine HCl, Drug Layered Beads	Batch Number: 837AG034		Date: [redacted]
Physical Description: Off White	Capsule Size: N/A		Batch Size: 7500.0 gms
Imprint (Uppers): N\A	Imprint (Lowers): N\A	Label (mg\Unit): N/A	Unit Weight (mg): N/A
Written By: A.Gallo [signature]	Reviewed By:	Room #: N92	Temperature: 16.0 °C Humidity: 32.0 % Time: 7:30 AM

ITEM #	Ingredients (Trade Name Grade)	Raw Material Lot #	Quantity %	Quantity Mg\Unit	Quantity Gm\batch	Quantity Weighed	Weighed By	Checked By	Date Weighed
1	*Cyclobenzaprine HCl	C14607401	25.00	7.50	1875.0 gm	1875.0	AE		[redacted]
2	Sugar Spheres 20 – 25 Mesh (Hansen)	RD – 991114	73.00	21.90	5475.0 gm	5475.0	AE		
3	**Opadry Clear YS – 1 – 7006	H10507376	2.00	0.60	150.0 gm	150.0	AE		
4									
5									
6									
7									
8									
9									
10	Acetone, NF 50/50 % Ratio	A10707332			2812.50 ml	2812.50	AE		
11	USP Purified Water, 50/50 % Ratio	W-10002061B			2812.50 ml	2812.50	AE		
12	USP Purified Water @ 10.0 % of Seal Coat	W-10002061B			1350.0 ml	1350.0	AE		
	Total:		100.00	30.00	7500.0 gm	7500.0	AE		

Objective: to evaluate dose @ 25.0 % Using GPCG 5

Note: Acetone, NF / USP Purified Water 50/50 Ratio.

* Item #10,11, 12 is use to make coating solutions. Both mg\ unit and g\ batch totals do not reflect entries.

Exhibit A

Exhibit B

Project No._____

TITLE CYCLOBENZAPRINE HCl EC BEADS. Book No. 805

From Page No. 105

Purpose: To EC coat Cyclobenzaprine HCl drug layered beads using solvent (90:10) Acetone : H_2O as a medium. The drug layered beads were then Ethyl Cellulose coated using Acetone : H_2O (98 : 2). The EC was done using Glatt GPCG-5 Duster.

Master Formula

Page 1 of 1

Product Name: Cyclobenzaprine HCl – Extended Release Beads (25.0 mg)

Physical Description : Extended Release Coating

Lot # 805-AAA-105

Date : [redacted]

Ing. #	Ingredients (Trade Name Grade)	Rev Material Lot #	Quantity % W/W	Quantity Mg/Unit	Quantity Gm/batch	Quantity Weighed	Weighed By	Checked By
1.	Cyclobenzaprine HCl, Drug Layered Beads	837-A0-034	3600.0			3600.0	AAA	
2.	Ethylcellulose 10P Premium (10cps), NF	B11407226	363.6			364.0	AAA	
3.	Diethyl Phthalate, USP	D11807500	36.4			36.4	AAA	
10.	Acetone, NF (95 parts)	A10707552	5639.0			5639.0	AAA	
11.	Purified Water, USP (2 parts)	W100-01	115.0			115.0	AAA	
	Total:							

Objective: Evaluating Dose @ 16.6 % Samples were taken @ 7, 8, 9, & 10% of EC applied.

AAA [redacted]

To Page No

Witnessed & Understood by me, Date [redacted] Invented by Anthony A-Appi Date [redacted]

Project No. —
TITLE Cyclobenzaprine HCl [illegible] Book No. 891

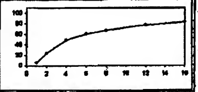
From Page No. 112 [signature] [redacted]

** For System Suit See p. 114

[redacted]				[redacted]	[redacted]		[redacted]	[redacted]
Stability Condition:	N/A			Std 2 Dilution (mL):	1000			
Reference:	NB891,P104			Std 2 Conc. (mg/mL):	0.03043			
				Std1 = 0.0306 mg/mL **				
Vessel	Weight (mg)	Active Wt (mg)		Actual Assay:	22.1			
1	140.95	31.15						
2	141.86	31.35						
3	142.03	31.39						
4	139.26	30.78						
5	141.04	31.17						
6	140.07	30.96						

Info	Area	Std Avg.	(%) Released	Avg. (%) Release	σ_{n-1}	(%) RSD	Spec.	Pass/Fail
Std 1	523879							
1.1	36087		6	6	0.5	9.1	F/O	F/O
1.2	37241		6					
1.3	31848		5					
1.4	31505		5					
1.5	34893		6					
1.6	33750	(Std 1&2)	6					
Std 2	524333	524106						
2.1	149530		25	24	1.0	4.2	NMT 40%	PASS
2.2	151988		25					
2.3	136393		23					
2.4	135862		23					
2.5	146873		25					
2.6	148717	(Std 2&3)	25					
Std 3	523832	523983						
4.1	291002		49	48	1.3	2.8	30% - 60%	PASS
4.2	293095		49					
4.3	277113		46					
4.4	274032		47					
4.5	293105		49					
4.6	287012	(Std 3&4)	48					
Std 4	524619	524126						
6.1	363326		61	60	1.4	2.3	F/O	F/O
6.2	364024		60					
6.3	351436		58					
6.4	340831		58					
6.5	364481		61					
6.6	356000	(Std 4&5)	60					
Std 5	528539	526579						
8.1	409548		68	67	1.5	2.3	60% - 80%	PASS
8.2	410539		68					
8.3	395003		65					
8.4	387491		65					
8.5	408278		68					
8.6	403270	(Std 5&6)	66					
Std 6	526866	527698						
12.1	469066		78	77	1.2	1.5	F/O	F/O
12.2	463710		77					
12.3	456293		76					
12.4	446242		75					
12.5	468754		78					
12.6	458622	(Std 6&7)	77					
Std 7	525680	526266						
16.1	504595		84	83	1.0	1.2	NLT 75%	PASS
16.2	504335		84					
16.3	491652		82					
16.4	483635		82					
16.5	501954		84					
16.6	501349	(Std 7&8)	84					
Std 8	526741	526211						

Sample	Time	Avg. Rel'd (%)	RSD
[redacted]05-AAA-105-10	1.0	6	9.1
N/A	2.0	24	4.2
	4.0	48	2.8
	6.0	60	2.3
	8.0	67	2.3
	12.0	77	1.5
	16.0	83	1.2



[illegible]-AAA-105-7 and 105[illegible]-AAA-105-10 Mon 10/15/01 [illegible]

16 h
$$\% \text{ Released} = \frac{(501349)}{(526211)}\frac{(0.03043\ mg/mL)(900\ mL)(100)}{(140.07\ mg)(22.1\%/100\%)} = 84.3\% \approx 84\%$$

Chromatograms stored in Box 891

To Page No. [illegible]

Witnessed & Understood by me, [signature] | Date [redacted] | Invented by ______ | Date [redacted]
Recorded by [signature]

ISSUED BY Q.A.

Eurand America, Inc.
Cyclobenzaprine HCl ER Beads
Batch Size: 85 kg (Theoretical)
MF #: A-50PE271-A

Lot #: PE271EA001	Date of Manufacturing: [redacted]
Effective Date: [redacted]	
Prepared By:	Date:
Mfg. Approval By:	Date:
R&D Approval By: Phil Perel	Date:
QA Approval By:	Date:
QA Issue:	Date:
QA Audited By:	Date:

[redacted]

Item No.	Item Code	Bead Dosage (mg/g)	% per Batch (w/w)	Ingredient Name	Theoretical Quantity Per Batch**
1	PE249	910.00	91.00	Cyclobenzaprine HCl Intermediate Beads	77.4 Kg
2	E114	81.25	8.13	Ethylcellulose, Premium Std 10cps	6.9 Kg
3	D118	8.75	0.88	Diethyl Phthalate, NF	0.75 Kg
4	A107 -	—	—	Acetone, NF*	116.7 Kg
5	W100	—	—	Purified Water, USP*	2.4 Kg
		1000.00	100.01	TOTAL=	85.0 Kg

*Removed from process during the drying process
**Actual batch is based on the actual quantity of the Intermediate Beads available for use. See page 2

ISSUED BY Q.A.

Eurand America, Inc.
Cyclobenzaprine HCl MR Capsules, 30 mg
Batch Size – 130,000 Capsules (Theoretical))
MF#: A-60PF306-A

Lot # PF306EA 001	**Date of Manufacturing:** [redacted]
Effective Date: [redacted]	
Prepared By:	**Date:** [redacted]
MFG. Approval By:	**Date:**
R&D Approval By:	**Date:**
QA Approval By:	**Date:**
QA Issue:	**Date:**
QA Audited By:	**Date:**

Item Code	Item No.	mg per capsule	% per Capsule (w/w)	Ingredient Name	Quantity per Batch
GI34	1	37.00[1]	21.91	White, Opaque Hard Gelatin Capsules, Size 4,	4.81 kg
PE271	2	131.87[2]	78.09	Cyclobenzaprine HCl Extended Release Beads	17.14kg
[redacted]	Total	168.87	[redacted]	[redacted]	21.95 kg

[1]Based on a theoretical empty capsule weight of 37.0 mg

[2]Equivalent to 30 mg of Cyclobenzaprine Hydrochloride (Beads based on a theoretical assay of 22.75%)

Exhibit E

Exhibit F

Cyclobenzaprine 30mg MR Capsules
Lot# PF306EA001

1 hour				Avg. STD
CHKSTD	262100	CHKSTD	256778	259438
1	10845	7	14041	
2	5836	8	14419	
3	12708	9	0	
4	11645	10	14435	
5	11232	11	15283	
6	10480	12	13404	
CHKSTD	256775	CHKSTD	262386	259581

2 hour				
CHKSTD	262388	CHKSTD	263549	262944
1	73230	7	83060	
2	80480	8	84176	
3	80622	9	81274	
4	77577	10	84348	
5	81304	11	78231	
6	80205	12	85540	
CHKSTD	263589	CHKSTD	262181	262690

4 hour				
CHKSTD	262181	CHKSTD	261515	261853
1	138053	7	150268	
2	143494	8	156286	
3	145169	9	151016	
4	143021	10	156610	
5	149223	11	149047	
6	145148	12	150601	
CHKSTD	261515	CHKSTD	261866	266067

8 hour				
CHKSTD	262252	CHKSTD	262598	262425
1	182178	7	187179	
2	181272	8	184560	
3	182435	9	184135	
4	187995	10	187020	
5	188802	11	184727	
6	190602	12	184823	
CHKSTD	266252	CHKSTD	263363	264808

8 hour				Avg. STD
CHKSTD	263363	CHKSTD	270750	267057
1	205865	7	220888	
2	215910	8	218838	
3	216016	9	205793	
4	211804	10	218400	
5	220533	11	211188	
6	214893	12	222246	
CHKSTD	270750	CHKSTD	263356	267053

12 hour				
CHKSTD	263356	CHKSTD	261737	262547
1	232004	7	247858	
2	246230	8	243567	
3	246103	9	230755	
4	245046	10	249980	
5	261809	11	237970	
6	244480	12	252555	
CHKSTD	261737	CHKSTD	261580	261664

16 hour				
CHKSTD	261890	CHKSTD	261252	261421
1	247344	7	264019	
2	262134	8	262718	
3	263803	9	242544	
4	256431	10	265913	
5	258489	11	254622	
6	265068	12	259002	
CHKSTD	261252	CHKSTD	262478	261864

STD conc	0.03007	mg/ml	
Strength	30	mg	

1 hour (FIO)				
1	4	7	5	
2	2	8	5	
3	4	9	0	
4	4	10	5	
5	4	11	5	
6	4	12	5	
Average:	4 %			

2 hour (0 - 40%)				
1	25	7	29	
2	28	8	30	
3	28	9	28	
4	27	10	29	
5	28	11	27	
6	28	12	29	
Average:	28 %		Pass	

4 hour (10 - 60%)				
1	47	7	54	
2	48	8	54	
3	50	9	52	
4	49	10	54	
5	51	11	51	
6	50	12	50	
Average:	51 %		Pass	

8 hour (FIO)				
1	61	7	67	
2	65	8	66	
3	65	9	63	
4	63	10	67	
5	67	11	64	
6	64	12	66	
Average:	65 %			

8 hour (60 - 80%)				
1	69	7	76	
2	73	8	74	
3	73	9	70	
4	72	10	74	
5	74	11	71	
6	73	12	75	
Average:	73 %		Pass	

12 hour (FIO)				
1	80	7	85	
2	84	8	85	
3	85	9	80	
4	84	10	86	
5	86	11	82	
6	84	12	87	
Average:	84 %			

16 hour (65.T 75%)				
1	85	7	91	
2	90	8	91	
3	91	9	84	
4	88	10	92	
5	93	11	89	
6	91	12	93	
Average:	90 %		Pass	